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EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/078,949	CROOKE, STANLEY T.	
	Examiner	Art Unit	
	Sean R. McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *165,167-183 and 202-258* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *165,167-183 and 202-258* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/23/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 5/23/08 has been entered.

Claims 165, 167-183, and 202-258 are pending and under examination.

Applicants submission of 5/23/08 includes an information disclosure statement and also includes amendments to the claims.

The new rejections below are in response to the submission filed 5/23/08 and for new considerations of double patenting.

The information disclosure statement filed 5/23/08 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because reference "59" has no date and does not appear to be a publicly available publication. It has been placed in the application file, but the information referred to therein as "59" will not be printed on any patent that may issue from this application. The information in reference "59" however

has been considered by the examiner. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims165, 167-183, and 202-258 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,107,094. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant method of activating a double

stranded nuclease via a double stranded nucleic acid is anticipated and made obvious by the claims of the patent. The instant claims are drawn to activating a double stranded RNA nuclease by contacting the nuclease with a double stranded nucleic acid with specified modifications. The methods of the patent are drawn to modification of a target RNA with the addition of a modified RNA oligonucleotide where the claims embrace such modification in a cell/organism or *in vitro* where the mechanism of modification is disclosed in the patent as cleavage by a double stranded RNA nuclease. The claims and specification disclose the nature of the target RNA and the targeting nucleic acids including size ranges and modifications where these modifications and size ranges are specifically recited in the instant claims. The patent, for example exemplifies an embodiment where both oligonucleotides are the same length and both are modified. Since the patent describes all of the same size ranges and modifications where the mode of activating (the instant claims) and modification (the patent) both include cleavage of a double stranded nucleic acid where both the instant claims and the patent claims embrace the same double stranded RNA targets/substrate of a double stranded RNA nuclease. The instant specification nor the patent define an "oligonucleotide" such that a second "oligonucleotide" would exclude an mRNA target, for example. The context of the claims also does not exclude or make unreasonable the preceding assertion.

Claims 165, 167-173, 175, 179, 180 and 236-246 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 43-47 of U.S. Patent No. 5,898,031. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant method of activating a double stranded nuclease via a double stranded nucleic acid is anticipated and made obvious by the claims of the patent. The instant claims are drawn to activating a double stranded RNA nuclease by contacting the nuclease with a double stranded nucleic acid with specified modifications. The methods of the patent are drawn to modification of a target RNA with the addition of a modified RNA oligonucleotide where the claims embrace such modification in a cell/organism or *in vitro* where the mechanism of modification is disclosed in the patent as cleavage by a double stranded RNA nuclease. The claims [43-47] [but see also claims 1-42 and 48-66 drawn to a targeting oligonucleotide meeting all of the required modifications of the instant claims, for example] and specification of the patent disclose the nature of the target RNA and the targeting nucleic acids including size ranges and modifications where these modifications and size ranges are specifically recited in the instant claims. Since the patent describes all of the same size ranges and modifications where the mode of activating (the instant claims) and modification (the patent) both include cleavage of a double stranded nucleic acid where both the instant claims and the patent claims embrace the same double stranded RNA targets/substrate of a double stranded RNA nuclease. The instant specification nor the patent define an "oligonucleotide" such that a

second "oligonucleotide" would exclude an mRNA target, for example. The context of the claims also does not exclude or make unreasonable the preceding assertion.

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Claims 165, 167-173, 175, 179, 180, and 236-246 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 43, 44, 94-104, and 135-145 of copending Application No. 10/281,349. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant method of activating a double stranded nuclease via a double stranded nucleic acid is anticipated and/or made obvious by the claims of the '349 application. The instant claims are drawn to activating a double stranded RNA nuclease by contacting the nuclease with a double stranded nucleic acid with specified modifications. The methods of '349 are drawn to cleavage of a target RNA with the addition of a modified RNA oligonucleotide and a contacting with a double stranded RNA nuclease where the claims embrace such modification in a cell/organism or *in vitro* where the mechanism of cleavage is disclosed in '349 as cleavage by a double stranded RNA nuclease. A double stranded RNA nuclease that cleaves is "activated". The claims and specification of both applications disclose the nature of the target RNA and the targeting nucleic acids including size ranges and modifications where these modifications and size ranges are specifically recited in the instant claims and in the claims of the '349 application. Since both applications patent describes all of the same size ranges and modifications where the mode of activating (the instant claims) and cleavage ('349) both include cleavage of a double stranded nucleic acid where both the

instant claims and the patent claims embrace the same double stranded RNA targets/substrate of a double stranded RNA nuclease. The instant specification nor the patent define an "oligonucleotide" such that a second "oligonucleotide" would exclude an mRNA target, for example. The context of the claims also does not exclude or make unreasonable the preceding assertion.

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is noted that the U.S Court of Appeals Federal Circuit decision in *Pfizer Inc. V. Teva Pharmaceuticals USA Inc.*, 86 USPQ2d 1001 (Fed. Cir. 2008), makes it clear that the protection afforded by 35USC 121 applies only to divisional applications filed as a result of a restriction requirement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 165, 167, 173, 175, 179, 180, and 236-246 are rejected under 35 U.S.C. 103(a) as being unpatentable over Metelev et al [WO 94/02498, cited on IDS filed 5/23/08].

The claimed invention is drawn to the activation of a double stranded RNA nuclease via contacting the nuclease with a double stranded nucleic acid where the double stranded nucleic acid comprises specified modifications. For the purposes of applying the prior art the following is noted. The instant claims can reasonable be construed to include methods where a nucleic acid (antisense) is administered to a cell where the nucleic acid (antisense) binds its target and forms a double stranded RNA which now in the presence of a cell containing a double stranded nuclease activates the double stranded RNA nuclease. It is noted that the context of the instant claims and the instant specification does not prohibit or make unreasonable an interpretation were one of the oligonucleotides is an mRNA. The instant specification does not appear to provide a definition of oligonucleotide where an mRNA would be excluded.

Metelev teaches antisense oligonucleotides that are hybrid oligonucleotides. The disclosure of Metelev does not provide a specific embodiment of the instantly claimed

invention, but does provide teachings where the instant invention would be an obvious embodiment. Metelev teaches the construction of hybrid oligonucleotides to test for antisense compounds that have desirable properties such as nuclease resistance and/or duplex stability and or RNase activation (see page 5-8 and Table I, for example). It is taught at page 8 that to analyze and explain the importance of each of these parameters to the effectiveness of antisense oligonucleotides, it is necessary to have oligonucleotides that vary in each of these parameters. At page 11 it is taught;

"A third feature of oligonucleotides according to this aspect of the invention is the presence of ribonucleosides, 2,-substituted ribonucleosides or combinations thereof. For purposes of the invention, the term ,,2,-substituted" means substitution of the 2'-OH of the ribose molecule with, e._=~, 2'-OMe, 2'-allyl, 2'-aryl, 2'-alkyl, 2'-halo, or 2'-amino, but not with 2'-H, wherein allyl, aryl, or alkyl groups may be unsubstituted or substituted, e.__-g~, with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy, carboxyl, carbalkoxyl or amino groups. Oligonucleotides according to the invention contain at least one ribonucleoside and/or 2,-substituted ribonucleoside. In a preferred embodiment, such oligonucleotides have 6 or more ribonucleosides and/or 2'-substituted ribonucleosides to enhance duplex stability. Such ribonucleosides and/or 2,-substituted ribonucleosides can be present singly, in pairs, or in larger contiguous segments, and may be present at any position within the oligonucleotide or at multiple positions within the oligonucleotide. Such ribonucleosides and/or 2'-substituted ribonucleosides may comprise as many as all but one nucleoside within the oligonucleotides. Thus, in a preferred embodiment, having from about 2 to about 50

nucleosides or most preferably from about 6 to about 50 nucleosides, the number of ribonucleosides or 2'- substituted ribonucleosides will range from about I to about 49 deoxyribonucleosides. The ability to vary the numbers and positions of phosphorothioate and/or phosphorodithioate internucleotide linkages, deoxyribonucleosides, and ribonucleosides or 2,-substituted ribonucleosides allows the investigator to examine in detail how each of these variables affects the parameters of nuclease resistance, duplex stability and RNase H activation. The ability to vary the size of the oligonucleotide allows examination of yet another parameter. In addition, smaller oligos (e.g., dimers) can be used as building blocks for larger oligos. Thus, every such possible embodiment described above is useful in such studies."

The teaching above clearly provide for embodiments that would provide antisense mRNA targets that are substrates for a double stranded RNA nuclease. Since the purpose of the antisense taught by Metlev et al is to provide hybrid antisense oligonucleotides that can target disease associated genes or viral genes it would have been obvious to test these antisense in cells including human cells, which contain double stranded RNA nucleases, such as was done by Metlev in their Example 5. It is noted that the limitation of detecting activation of a double stranded RNA nuclease would be met with the observation of reduced target gene expression or some other physiological effect on the cells presented by an antisense oligonucleotide. In this rejection it is noted that all of the steps have been met without needing to know that the oligonucleotides of the prior art are substrates to a double stranded RNA nuclease. The

motivation to provide the modified double stranded target in a cell may be different, but still does provide for making and using antisense oligonucleotides modified as required by the instant claims that bind to an mRNA target forming a double stranded oligonucleotide that is a substrate for a double stranded RNA nuclease in cells that would contain double stranded RNA nucleases, where the expected observed effect of inhibition of the mRNA expression would be due to activation of a double stranded nuclease, but would still be the expected effect even if it was not known that a double stranded nuclease RNA nuclease provided for the observed effect.

The invention as a whole would therefore have been prima facie obvious to one in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sean R McGarry
Primary Examiner
Art Unit 1635

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Primary Examiner, Art Unit 1635